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A Close-to-Aromatize Approach for the Late-Stage Functionalization through Ring Closing Metathesis

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An efficient approach for the synthesis of monosubstituted aromatic compounds relying on a ring-closing metathesis followed by spontaneous 1,2-elimination is presented. The efficiency for late-stage functionalization is highlighted in various solvents (up to 920 TON). This approach is compatible with strained cycles and other multiple bonds in the substrate.

Keywords: elimination, late-stage functionalization, metathesis, ring closing metathesis.

Introduction

Aromatic fragments are present in a vast majority of organic compounds. For the late-stage introduction of aromatic fragments, common methods include various cross-coupling and C–H activation strategies.[1–6] Herein, we exploit ring closing metathesis of a readily accessible triene-ol to access monosubstituted benzene derivatives.

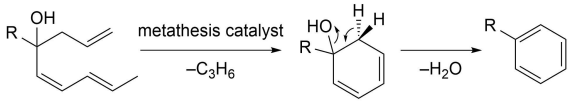
Numerous strategies to produce aromatic rings as a result of ring-closing metathesis (RCM) have been reported.[7–14] Most of these, however, require harsh oxidants to produce the aromatic ring.[15–20] We were inspired by a report by *Sabatino et al.*[21] who reported a 'close-to-release' approach whereby aromatization resulting from a 1,4-elimination serves as driving force for the generation of naphthalene, with the concomitant release of a cargo-molecule. Herein we report our efforts to extend this methodology to RCM followed by the 1,2-elimination of water to generate monosubstituted benzene moieties (*Scheme 1*).

Results and Discussion

To test the generality of this approach, we identified the triene-one **1** as a key building block. Subsequently, a *Grignard*-type addition to the ketone functionality allows tethering this masked benzene to a variety of fragments.

Synthesis of (5*Z*,7*E*)-nona-1,5,7-trien-4-one **1** was carried out according to the general procedure reported by *Cossy* and coworkers that they used in the total synthesis of (−)-muricatacin and related compounds.[22] Reaction of *Weinreb* amide **2** with allyl-magnesium chloride afford triene **1** in >75% yield (*Scheme 2*). The γ,δ-double bond is highly reactive, which, together with the (Z)-configuration of the α,β-double bond, opens up the possibility of an intramolecular reaction.

The biphenyl precursor **3a** was selected for the optimization of the cyclization conditions. The reaction proceeds in low yields in polar solvents (*Table 1*, *Entries 1–3*), including in water using AquaMet as catalyst (*Table 1*, *Entries 4–6*). This may be traced back to



Scheme 1. Concomitant ring-closing metathesis followed by 1,2-elimination of water for the synthesis of monosubstituted benzene derivatives.

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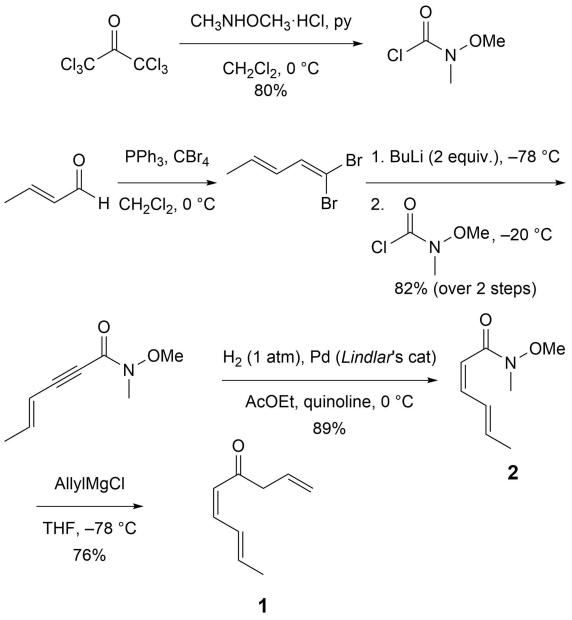


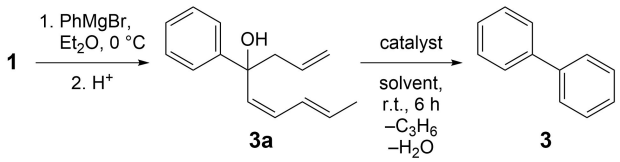
Scheme 2. Synthesis of (5*Z*,7*E*)-nona-1,5,7-trien-4-one **1**.

the very low solubility of the triene **3a** in aqueous media. The most effective solvent proved to be dichloromethane, in which all reagents are readily soluble. The reaction yield is affected by the nature of the catalyst, with the *Hoveyda-Grubbs* second-generation (HG-II) performing best (*Table 1*, *Entries 7–14*). Strikingly, the yield of biphenyl **3** increases with decreasing catalyst loading from 5 mol-% to 1 mol-%. This can be traced back to the cross-metathesis between the diolefinic substrate **3a** and the *ortho*-isopropoxy-benzylidene moiety of HG-II catalyst. The yield of this cross-metathesis product is affected by catalyst loading. The resulting disubstituted olefin does not further participate in productive ring-closing metathesis, thus contributing to erode the yield of biphenyl **3** with increasing catalyst loading.

Near quantitative conversion was achieved using 0.1 % catalyst, corresponding to >900 TON. ^{1}H-NMR Monitoring reveals that the equilibrium is reached after six hours at room temperature using 5 mol-% HG-II (*Figure 1*). To reach (near) full conversion, nine and twenty hours of reaction time are necessary using 1 mol-% and 0.1 mol-% HG-II, respectively (*Figure 1*).

With these optimized conditions at hand, monosubstituted benzenes **3**–**10** were synthesized without the requirement of isolating the alcohol resulting from the *Grignard* addition to (5*Z*,7*E*)-nona-1,5,7-trien-4-one (**1**). The syntheses were carried out in two steps: *1*) the reaction of ketone **1** with a *Grignard* derivative and

Table 1. Optimization of cyclization conditions.



Entry[a]	Solvent	Catalyst	Cat. load. [%]	yield [%][b]	TON
1	DMSO	HG-II	5	5 ± 1	1 ± 0
2	ACN	HG-II	5	20 ± 4	4 ± 1
3	Acetone	HG-II	5	26 ± 6	5 ± 2
4	DMSO/H_2O	AquaMet	5	n.d.	0
5	ACN/H_2O	AquaMet	5	3 ± 0	1 ± 0
6	Acetone/H_2O	AquaMet	5	9 ± 4	2 ± 1
7	CH_2Cl_2	G-I	5	58 ± 5	12 ± 1
8	CH_2Cl_2	G-II	5	63 ± 6	13 ± 1
9	CH_2Cl_2	HG-I	5	71 ± 9	14 ± 2
10	CH_2Cl_2	Umicore-M1	5	57 ± 7	11 ± 1
11	CH_2Cl_2	*Schrock*[c]	5	35 ± 1	7 ± 0
12	CH_2Cl_2	HG-II	5	92 ± 3	18 ± 1
13	CH_2Cl_2	HG-II	1	97 ± 2	97 ± 2
14	CH_2Cl_2	HG-II	0.1	92 ± 4	920 ± 40

[a] Reaction conditions: solvent (1 M), catalyst, r.t., 6 h. [b] Yields were determined by ^{1}H-NMR as the average of three independent experiments. [c] 2,6-Diisopropylphenylimidoneophylidene molybdenum(VI) bis(hexafluoro-*tert*-butoxide).

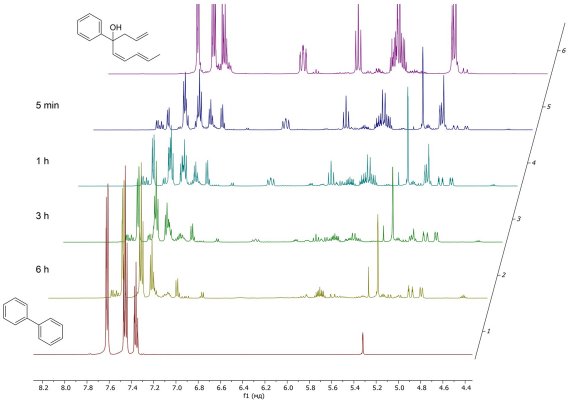
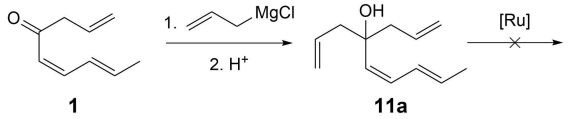


Figure 1. ^{1}H-NMR Monitoring of the cyclization (CH_2Cl_2, 1 M), 5 mol-% HG-II, r.t.). None of the diene-ol intermediates is detected by ^{1}H-NMR.



Scheme 3. Evaluating the regioselectivity of RCM using tetraene-ol **11a**.

2) ring-closing metathesis with spontaneous 1,2-elimination of H_2O (*Table 2*).

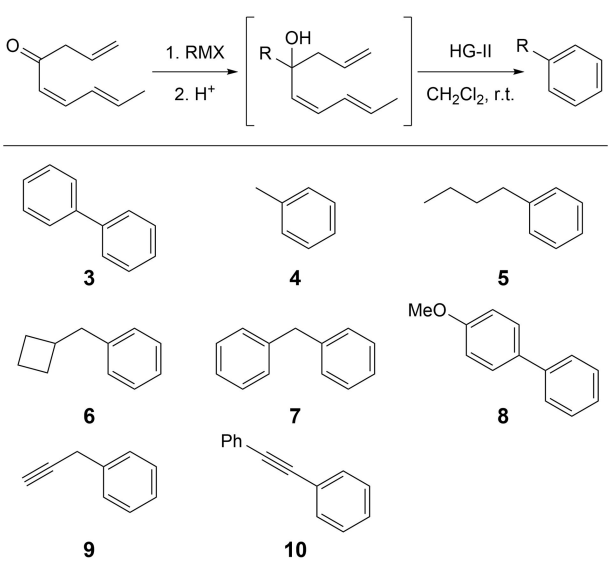
The metallated substrates were obtained from the corresponding halides and alkynes by adding either Mg or BuLi in ether. The monosubstituted benzene products **3**–**10** resulting from RCM and 1,2-elimination were isolated by column chromatography. Gratifyingly, the above reaction sequence tolerates a variety of (cyclic) aliphatic and aliphatic substituents, including cyclobutane (*Table 2*, *Entries 1*–*6*). Alkynes do not participate in metathesis as no product mixtures could be detected (*Entries 7* and *8*).

The regioselectivity was evaluated by subjecting the tetraene-ol substrate **11a** to RCM. Under standard conditions (CH_2Cl_2, 1 M), 5 mol-% HG-II, r.t.), no RCM product was detected. Upon increasing catalyst loading to 50%, only cross-metathesis with the styrene fragment of the HG-II catalyst could be isolated, along with the starting material **11a**. We could not find any rationale for this unexpected lack of reactivity (*Scheme 3*).

Conclusions

An efficient method for the synthesis of monosubstituted aromatic compounds with saturated and unsaturated aliphatic and aromatic substituents was developed. The key step proceeds in almost quantitative yields with low catalyst loading (0.1 mol-%, up to 920 TON). This method can be used to introduce an aromatic moiety at a late stage if alternative cross-coupling schemes prove challenging. The synthesis of the key intermediate can be carried out on a multi-gram scale with a total yield of >52% over five steps. The strategy outlined herein, relying on more elaborate *Weinreb* amides,[22,23] should allow to introduce various poly-substituted benzene moieties as a result of ring-closing metathesis. The strategy to introduce a masked benzene moiety as a result of RCM is limited by the following features: *1*) The substrates must not contain any functional group that can interfere with the metalating reagent and *2*) The

Table 2. Substrate scope for the synthesis of monosubstituted benzene derivatives through RCM.



Entry[a]	RMX	Product	Yield [%] (over 2 steps)[b]
1	MeMgI	**4**	65
2	BuMgBr	**5**	78
3	cyclobutyl-CH_2MgBr	**6**	56
4	BnMgBr	**7**	75
5	PhMgBr	**3**	83
6	*p*-MeOPhMgBr	**8**	72
7	HC≡CCH_2MgBr	**9**	70
8	PhC≡CLi	**10**	47

[a] The first step was carried out with ketone **1** and corresponding *Grignard* reagent (diethyl ether (0.5 M), 0 °C, 2 h) without isolating the corresponding trien-4-ol. The second step was performed with crude alcohols using HG-II catalyst (5 mol-%) in CH_2Cl_2 (1 M) for 6 h. [b] Yield of isolated product.

metalated derivative must have sufficient nucleophilicity to react with the carbonyl group of the unsaturated ketone.

We are currently capitalizing on this strategy to generate drugs *in vivo* (*e.g.* tamoxifen) as a result of ring-closing metathesis from inactive precursors.[21]

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Author Contribution Statement

T. R. W. and *B. L.* designed the concept. *T. R. W.* supervised the work which was carried out by *B. L.*; *B. L.* and *T. R. W.* discussed the results and wrote the manuscript. Both authors have given approval to the final version of the manuscript.

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